Enhanced Knowledge in Sciences and Technology Vol. 2 No. 1 (2022) 481-490

EKST

Homepage: http://publisher.uthm.edu.my/periodicals/index.php/ekst
e-ISSN : 2773-6385

Mathematical Modeling in Tumor Growth Using Gompertz Model

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DOI: https://doi.org/10.30880/ekst.2022.02.01.052
Received 02 January 2022; Accepted 02 March 2022; Available online 1 August 2022

Abstract: This project focuses on how differential equation helps the formulating mathematical model of tumor growth by using Gompertz model. The Gompertz model is used to analyse the growing glioblastoma (brain tumor) data over seventy days in order to determine how accurate the growth over time outcomes are. The tumor data is graphed in Excel alongside the values from the Gompertz equation. The Excel solver is used to determine the constant values of α, β and C. The data from the tumor closely resembles the outcome of the Gompertz model with sigmoidal "S" curve. The Gompertz method is applied to data from a brain tumor's development over seventy days to compare the method's accuracy to real-world results and determine the tumor's maximum volume of growth.

Keywords: Tumor, Gompertz Model, Maximum Tumor Volume

1. Introduction

Cancer is a term used to refer to a disease characterized by abnormal cell growth that divides uncontrollably and potentially invades other tissues in body. Historically, the origin of the word cancer is credited to a Greek physician. Hippocrates used the terms "carcinos" to describe several types of cancer [1]. Cancer occurs due to mutational changes or damage to the genetic material of deoxyribonucleic acid (DNA) in cells [1]. Each cell contains individual genetics that have a set of indicators that tell the function of each cell, including the timing of cell growth and division. Errors in instructions or information can cause existing cells to grow out of control, a condition that leads to cancer.

Tumor can be either benign or malignant. A benign tumor is a mass of cells that do not spread to the other part of the body. The benign tumor grows slowly and is not harmful, so it is not cancerous meanwhile a malignant tumor is one that is cancerous. It is a collection of cells with the ability to spread to other parts of the body or infect surrounding tissues and destroy them. The lymphatic system or bloodstream is the pathway for cancer cells spread to the other parts of the body. This is how cancer

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cells spread from the primary tumor to generate new tumor (secondary tumor) in different organs, a process known as metastasis [2].

Cancer is one of the most dreaded diseases, as it is one of the top causes of death in both men and women of all ages. Breast cancer, colorectal cancer, lung cancer, lymphoma cancer, nasopharynx cancer, prostate cancer and ovarian cancer are examples of cancers that we often hear about.

At the intersection of mathematics and biology, the call to use mathematics to improve the predictive power of biological fields resounds. This century as in the twentieth should be devoted to making mathematics relevant to biology [3]. Many different models can be used to study cancer cell proliferation such as exponential model, Mendelsohn model, linear model, surface model, Bertalanffy model and Gompertz model [4]. Some of these include models with varying degrees of freedom, such as tumor size [5].

Mathematical models have been developed to help predict tumor size and comprehend the dynamical process of cancer cell development and proliferation. The use of differential equations has been proven to predict the growth curve of various types of tumors [5]. One model that has been successfully used to manage this prediction is Gompertz model. We chose the Gompertz model for this paper because of its simplicity and accuracy. According to Murphy H. *et al*, Gompertz model was shown to have the best fit for both clinical and experimental data for cancer [4]. Apply Gompertz method to data from a tumor's development to compare the method's accuracy to real-world results and to determine the tumor's maximum volume of growth. The first objective for this study is using differential equation to help provide the mathematical model in tumor growth. The second objective is to estimate the maximum tumor volume by using Gompertz model.

1.1 Causes of Cancer

In general, the immune system should always be able to detect the abnormal cells and kill them all the time including cancer cells. Failure during this task, the cell mass will grow out of control [6]. The immune system will act as a regular to ensure that failure cell is minimal and eliminated from the body system. A group of immune cells known as killer T cells (cytotoxic T cells) are among the immune cells responsible for monitoring the body system and removing damaged cells.

Besides that, smoking is the most important global cause of cancer. Smoking can lead to lung cancer, bladder cancer, mouth cancer, pharynx cancer, pancreas cancer, kidney cancer, stomach cancer, larynx cancer esophagus cancer and possibly colon cancer [7] [8]. According to Stephen S. Hecht, a cigarette contains a mixture of carcinogens, which stimulate the growth of cancer cells in the body [9].

Next, alcohol is one of the causes of cancer. Alcohol is an important cause of oral cancer, esophageal cancer, colorectal cancer, liver cancer [7]. According to William J. Blot, alcohol contains congeners and other contaminants that may be carcinogenic and be a catalyst for metabolic activation some compound into carcinogens [10]. Alcohol can act as a solvent to enhance the absorption of carcinogen to provide a mechanism to the interaction between alcohol and tobacco for involved in the development of mouth cancer, oral pharynx and extrinsic larynx [11].

Miguel Lopez-Lazaro discovered that cancer is produced by unregulated cell division of some cells, which results in the accumulation of aberrant cell populations [12]. The main biological cause of such excessive proliferation however has yet to be identified.

1.2 Treatment of Cancer

Even though tremendous progress has been made in medicine to enhance cancer therapy, but cancer still kills millions of people every year. Chemotherapy, surgery and radiotherapy are the most frequent cancer treatments available today [13]. Chemotherapy's purpose is to kill the cancer by

administering as much of the medicine as possible to the patient. As a result, the entire body is bombarded with medications, resulting in hair loss, diarrhea and nausea.

Until the 1960s, surgery and radiotherapy were the mainstays of solid tumor treatment [13]. Ionizing radiation is employed because it creates ions and deposits energy in the cells of the tissues it passes through, allowing it to damage and kill cancer cells [14]. Cancer cells that have had their DNA damaged beyond repair cease proliferating and eventually die.

After that, the use of nanoparticles for diagnosis, monitoring, control, prevention and treatment of diseases is characterized as nanomedicine, which is defined as the application of nanotechnology to the discipline of medicine [15]. Nanomaterials may be designed to interact with the body's immune system, as in cancer. According to Pucci *et al*, nanomedicine is described as material with a size of 1 to 1000 nanometers that are employed in cancer medicine to overcome some of the problems associated with conventional therapy [16]. Nanomedicine presents a way for delivering anti-cancer or immunotherapy medications more precisely while avoiding healthy tissues and minimizing many side effects.

1.3 Mathematical Model in Tumor Growth

To better comprehend the dynamical process of cancer cell proliferation, mathematical models have been developed. Deterministic models of exponential, logistic, Gompertz and Bertalanffy morphology have been widely used to model tumor growth. The model was designed to predict the rate of change in tumor volume over time. The Bertalanffy, Gompertz and logistic models share a common pattern of exponential models [17].

The exponential model is natural depiction of cancer progression in its early phases. In the exponential model, each cancer cell in the affected area splits into two daughter cells at a constant pace [4]. This model is concerned with the tumor's population rather than individual cells. However, when the population is very large, the increase in individuals is not significant compared to the overall population [1].

The logistic equation was first introduced by Pierre Francois Verhulst in 1883 said that the growth rate declines linearly with size until it reaches zero at carrying capacity [4]. Bertalanffy model shows that tumor volume decreases with cell death and increases with respect to surface area. However, Bertalanffy model is not suitable for predicting the progression of cancer proliferation [17].

Benjamin Gompertz created the Gompertz model in 1825 to explain the human mortality curves and determine the value of life insurances [17]. The Gompertz model is a generalization of a logistic model with an asymmetric curve with inflection points. It has an S-cuvre, it ultimately applied to model the size of cell growth in the entire organisms [17]. The modified Gompertz equation has good predictive ability to explain both unhindered tumor growth and hindered tumor growth and can be used to determine appropriate treatment [18]. The Gompertz model is based on a differential equation that is used to calculate growth rates in a variety of fields and it is extremely useful in explaining tumor dynamics [19].

2. Materials and Methods

2.1 Research Design

The focus of this study is on tumor growth models using ordinary differential equations (ODE). Many ordinary differential equation model have been proposed to indicate tumor growth and are used regularly to predict the efficacy of tumor growth. Quantitative research method has been use in this study to make this study a success. This method is use to achieve the two objectives of the study that have been identified which are using differential equation to help provide the mathematical model in tumor growth and to find maximum tumor volume. The classical Gompertz differential equation is

$$\frac{dV}{dt} = \alpha(\ln \beta - \ln V)V \qquad Eq.1$$

where V= volume in cubic milimetres, t=time, α and β = constant rate.

After that, to find the close values of the constant which are α, β and C requires a first guessing estimate. The Gompertz equation is entered into Excel with the constant values and each brain tumor data points to calculate the residual that used to determine the value of constants, α, β and C. The Gompertz method values are then plotted alongside the brain tumor data on the same graph to see how closely the method matches the actual values.

2.2 Sample Data

For the normal patient, information on cancer development is typically recorded just a single time or twice since Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) examines are over the top expensive. For research purposes, researchers have devised a battery of tests in which a growth is monitored on a regular basis in order to gather information on the rate of development and the behavior of specific types of disease. This examination project's filed guide has recovered data from one of the studies that focused on the treatments of glioblastoma. Glioblastoma is an aggressive type of cancer that can develop in the brain or spinal cord [19]. This is a type of brain tumor that grows quickly and with great force. The data consists of 15 observations [19]. The data set gathered on this tumor is the volumetric size over a seventy days' period.

2.3 Gompertz Model Formulation

Tumor growth patterns have been of interest to scientists since cancer research began and despite nearly a century of research, the exact growth rates or rather growth patterns, that represent solid tumors are still unknown. In 1825, Benjamin Gompertz developed the Gompertz model to explain human mortality curves. According to Gerlee, Gompertz had made the observation that "If the average exhaustions of a man's power to avoid death were such that at the end of equal infinitely small intervals of time, he lost equal portions of his remaining power to oppose destruction" [20].

The main driving force of the model is actuarial as a practical means of evaluating the value of life insurance, and serves as a model for its biological growth. Over the years, the common Gompertz model has become the preferred regression model for many types of organisms, including dinosaurs, birds, and mammals, including marsupials [21]. The Gompertz model is also often used to simulate the growth of the number or density of microorganisms, the growth of tumors, and the survival rate of cancer patients [21]. The Gompertz model is used to show the volume growth of tumors over time. It is based on an exponential formula, and the values generated by this formula are reasonably selected based on the behaviour of the tumor. According to the Stewart and Day [22], the Gompertz differential equation assumes that the tumors per volume growth rate decreases as the tumor volume increases.

To find the general solution for classical Gompertz differential equation from (Eq 1) need to assume $V \neq 0$ and $V \neq \beta$. Then, write the equation in differential form and integrate as

$$\int \frac{1}{V(\ln \beta - \ln V)} dV = \int \alpha \, dt \qquad Eq.2$$

Then integrate by using the substitution $u = \ln \beta - \ln V$ where $dv = -v \, du$.

$$-\int \frac{1}{u} du = \int \alpha \, dt \qquad Eq.3$$

$$-\ln|[\ln \beta - \ln V]| = \alpha t + C_1 \qquad Eq.4$$

$$\ln|[\ln\beta - \ln V]| = -\alpha t - C_1 \qquad Eq.5$$

After that, exponentiation both side to solve for V,

$$\ln\beta - \ln V = Ce^{-\alpha t} \qquad Eq.6$$

$$\ln\left(\frac{\beta}{V}\right) = Ce^{-\alpha t} \qquad Eq.7$$

$$\frac{\beta}{V} = e^{Ce^{-\alpha t}} \qquad Eq.8$$

The general solution for Gompertz model is

$$V = \beta e^{-Ce^{-\alpha t}} \qquad Eq.9$$

where
V= Volume in cubic milimetres
t= time in days
β= growth limit of the tumor
α=constant growth rate
C= constant rate of time

3. Results and Discussion

3.1 Estimation of Maximum Tumor Volume

Table 3.1 shows information on the volume size of brain tumor which is glioblastoma that occurs in that occurs in the brain and spinal cord over a period of seventy days from [19].

Table 1: Data set of volume size of brain tumor

Time (days)	Volume (V), mm^2
1	151
5	178
10	226
15	329
20	433
25	564
30	598
35	687
40	796
45	855
50	934
55	1001
60	1089
65	1143
70	1217

From those data, we can see tumor growth from every five days is increasing rapidly. So we will see the growth of these tumors by comparing it with the Gompertz model.

Figure 3.1 shows the data has been entered into Excel to see the type of graph it produces, which is a, “S” curve.

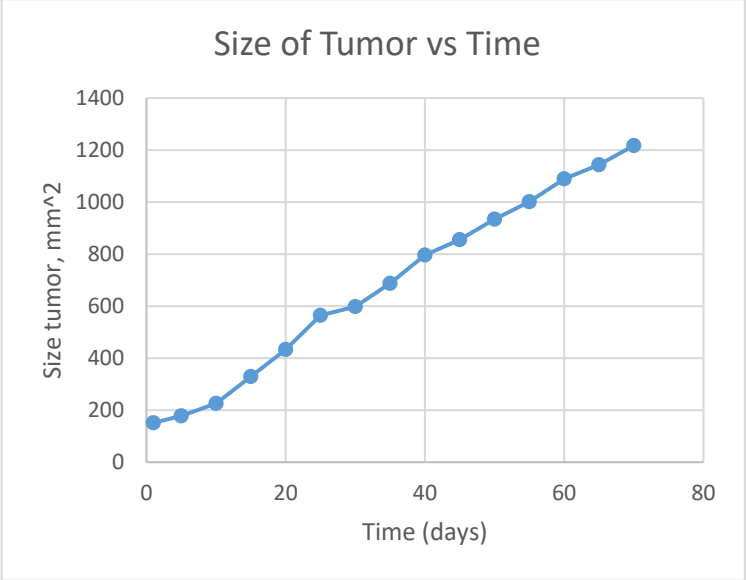

Figure 3.1: Graph of size of tumor (mm^2) vs time (days)

From Figure 3.1, we can clearly see that when the tumor size increases every five days. To find the maximum tumor volume, we need to know the values of constant which are α, β and C that correspond to the Gompertz equation (Eq.9). To find the constant values of α, β and C for the Gompertz model equation (Eq. 9). Estimated guesses are taken to find close values for the constants due to the scarcity of knowledge on the tumor. The residual is then used to assist in determining the values of the constants. The residual, which is the difference between the data set and the Gompertz value, is regarded as an error margin.

To estimate the value of constant growth rate, α, use this formula

$$growth\ rate = \left(\frac{present\ value}{past\ value}\right)^{\frac{1}{t}} - 1 \qquad Eq.10$$

where t represent time. Then, to estimate the value of constant rate of time, find the average of time which is five days divide by two are 2.5 days. To estimate the value of growth limit of tumor, insert the value of α and C into (Eq.9), $\beta = 1645.88$. Residual where used to guess the next estimate values.

In this study, the first estimate guess for the constant values is $\alpha = 0.05$, $\beta = 1645.88$ and $C = 2.5$.

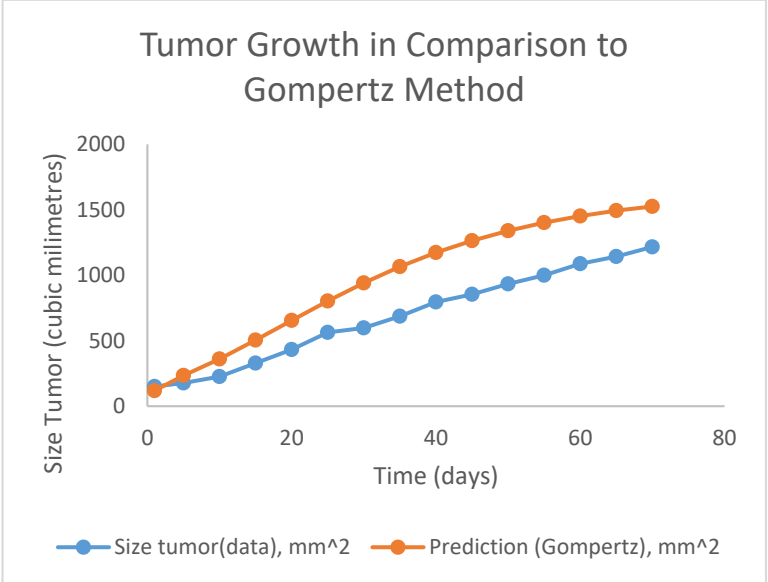

Figure 3.2: Tumor growth in comparison to Gompertz method with $\alpha = 0.05$, $\beta = 1645.88$ and $C = 2.5$

The sum of squared residuals for Figure 2 is 1411438.8491. The curve for the predicted data is very far from the curve for the observed data. The data from Gompertz method is higher than the observed data. So we can say that the first estimate guess for constant value are not suitable or does not correspond to the Gompertz equation (Eq 9). $\alpha = 0.02$, $\beta = 1550$ and $C = 2.5$ are the second approximate guesses for the value of the constant.

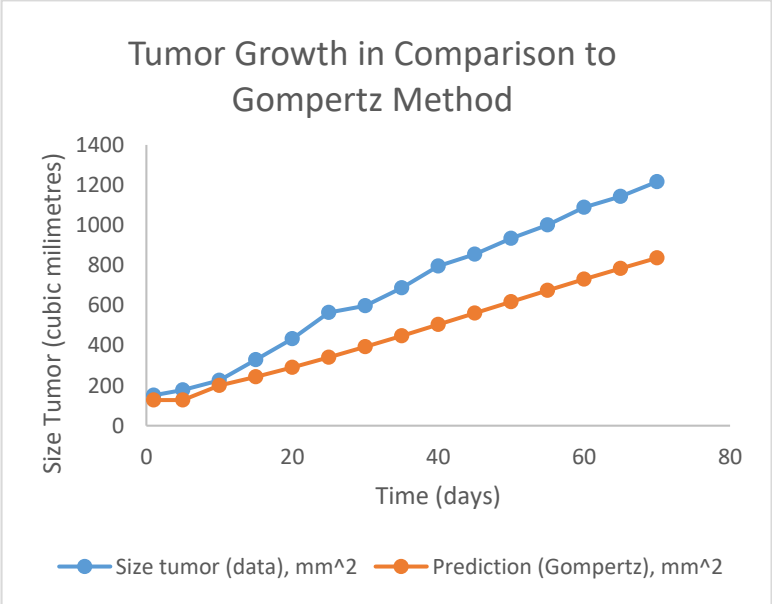

Figure 3.3: Tumor growth in comparison to Gompertz method with $\alpha = 0.02$, $\beta = 1550$ and $C = 2.5$

From Figure 3.3, the data from Gompertz method (orange curve) is lower than the observed data (blue curve). The sum of squared residuals is 961338.7147, also say that the second estimate guess for constant value are not suitable. For the third estimate guess for the constant value of α, β and C are 0.0321, 1555 and 2.4825 respectively.

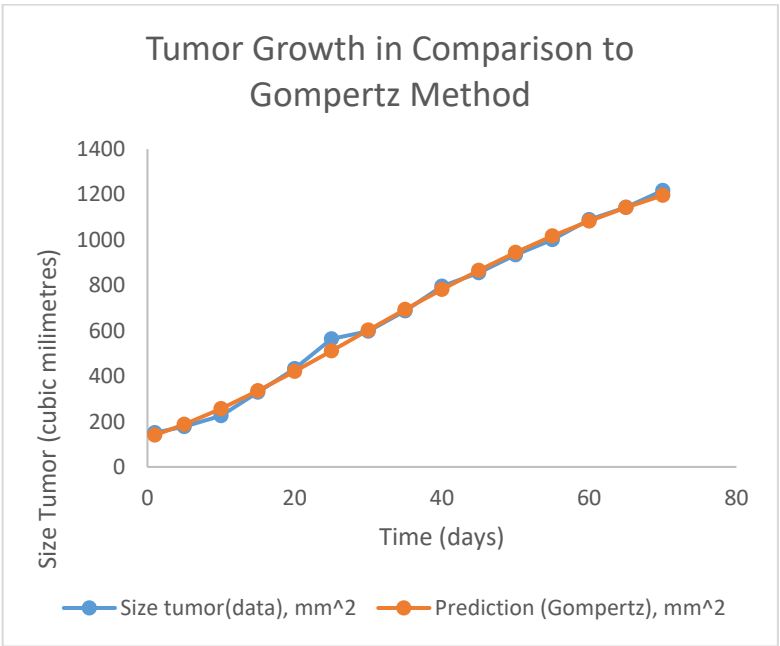

Figure 3.4: Tumor growth in comparison to Gompertz method with $\alpha = 0.0321$, $\beta = 1555$ and $C = 2.4825$

From Figure 3.4, we can see that the data from Gompertz method are almost matches the observed data. The sum of squared residuals for Figure 3.4 is 5353.8546. For the fourth estimate guess for the constant value of α, β and C are 0.0321, 1557.5989 and 2.4825 respectively.

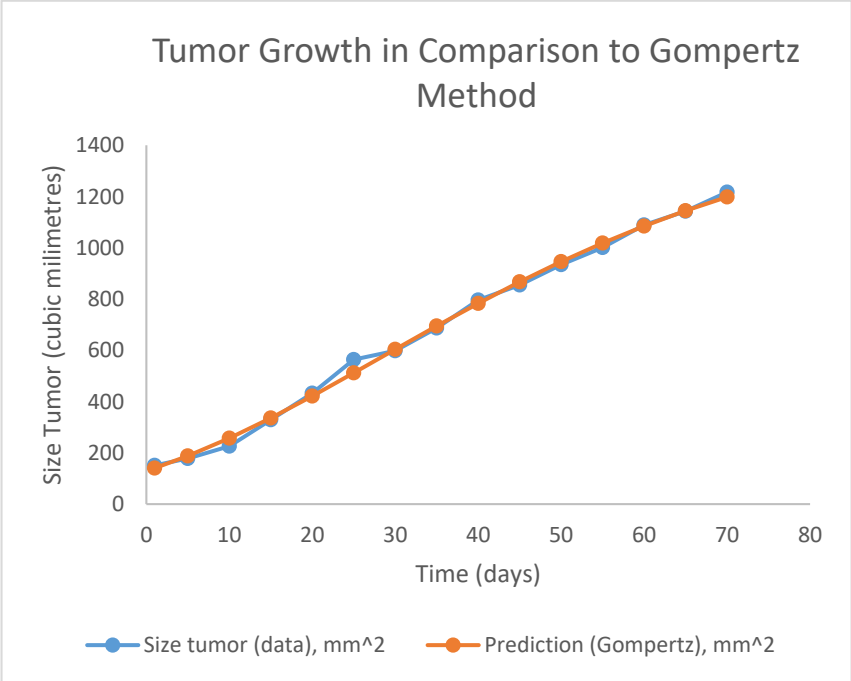

Figure 3.5: Tumor growth in comparison to Gompertz method with $\alpha = 0.0321$, $\beta = 1557.5989$ and $C = 2.4825$

From Figure 3.5, we can see that the data from Gompertz method is almost match the observed data. The sum of squared residuals for Figure 3.5 is 5305.3811. Figure 3.4 and Figure 3.5, show that both curve from Gompertz method is almost match the observed data. The third and fourth estimate guesses are acceptable. However the appropriate value of the constant is $\alpha = 0.0321$, $\beta = 1557.5989$ and $C = 2.4825$ because it has smaller the sum of squared residuals. Therefore, the Gompertz model for this brain tumor, using equation (Eq.9), is given by

$$V(t) = 1557.5989e^{-2.4825e^{-0.0321t}} \qquad Eq.11$$

The maximum growth limit of the brain tumor is $\beta = 1557.5989$ and the constant growth rate, $\alpha = 0.0321$ and the rate of time, $C = 2.4825$.

4. Conclusion

The first objective of this study is using differential equation to help provide the mathematical model of tumor growth is accomplished. The classical Gompertz differential equation to get the general solution of the model. The second objective of this study was also met, which was to determine the maximum volume for the brain tumor. This study has also successfully compared Gompertz method to brain tumor data to see if it would correlate similarly to depicting a sigmoidal curve on a graph.

The development pace of this growth is outrageous, expanding by practically 10% in 70 days. With such a rapid growth rate, there is significantly less of an opportunity to develop a treatment plan for the person suffering from this infection. These powerful growths are ideal for this technique because they allow us to predict the outcome of events and take action to prevent them from spreading. The eventual outcomes demonstrate the Gompertz method to be a right fit to gauge the remarkable development of a glioblastoma precisely. The maximum growth limit of the brain tumor, $\beta = 1557.5989$ and the constant growth rate, $\alpha = 0.0321$ and the rate of time, $C = 2.4825$.

Acknowledgement

The authors would also like to thank the Faculty of Applied Sciences and Technology, Universiti Tun Hussein Onn Malaysia for its support.

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